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Ellen M. Zaglaker GL5071H



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

COPY

APPLICANT: Wang et al)
SERIAL NO.: 07/179,100)
FILED: April 8, 1988)
TITLE: DNA SEQUENCES)
ENCODING)
OSTEOINDUCTIVE)
PRODUCTS)

GROUP ART UNIT: 185
EXAMINER: J. Ellis

December 12, 1990

Commissioner of Patents and Trademarks
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Applicants do not consider that the information listed is material to the patentability of the present invention. However, to ensure compliance with 37 CFR 1.56 and 1.97 Applicants wish to make this information of record. The documents described below are listed on accompanying PTO Form 1449 and a copy of each (otherwise noted) accompanies this statement. The full copies accompany the "Express Mail" copy.

Sen, US Patent 4,804,744 is understood to disclose a family of immunologically related osteogenic factors extracted from

demineralized bone matrix. The disclosed amino acid sequences of these factors do not share any homology with the proteins encoded by sequences of the present invention and are therefore considered to be different proteins. Sen, European Publication 148155 (not enclosed) corresponds to the above-described US Patent 4,804,744.

Seyedin et al, US Patents 4,774,228, 4,774,322, 4,810,691 and 4,843,063 disclose two cartilage-inductive factors (CIFS). These proteins have been characterized as TGF-B proteins. The disclosed amino acid sequences of these factors are different from the osteogenic proteins encoded by the DNA sequences of the present invention. European Publication 169016 (not enclosed) corresponds to these US patents 4,774,228 and 4,774,322.

Seyedin and Thomas, US Patent 4,434,094 discloses a process for partially purifying osteogenic factor from demineralized bone particles. The recovered fraction is less than or equal to 30,000 daltons. The proteins of the above identified patents '228 and '322 were purified to homogeneity using a purification procedure similar to that disclosed in 4,434,094 (see column 1, lines 50-62 of '228 and '322).

Seyedin and Thomas, US Patent 4,627,982 is understood to disclose a process for obtaining a partially purified proteinaceous bone inducing material containing proteins of molecular weight 10,000 to 30,000 daltons.

Nathan et al, U.S. Patent 4,563,350 discloses a composition which is a mixture containing an osteogenic factor (OF) protein derived from bone sufficiently free from impurities so as to be hypoimmunogenic. Nathan refers to a process described in Serial No. 630,938 for preparing OF. The above-described '228 and '322 patents disclose that the proteins described in 630,938 have been further described as TGF-b proteins.

Nathan et al, European Publication 0336760 discloses an osteogenically active protein. The protein sequence does not share homology with the proteins encoded by the DNA sequences of the present invention.

Urist, US Patent 4,294,753 is understood to disclose a process of separating bone morphogenic protein (BMP) from bone tissue. Urist US Patent 4,455,256 which is cumulative to '753 discloses the isolation of a mixture of proteins having a molecular weight of 1,000-100,000 daltons.

Urist, US Patent 4,761,471 and 4,789,732 are divisionals of Urist 4,619,989 previously discussed during prosecution. The disclosure in each of these patents is the same as in '989. '471 and '732 claim a process and product for inducing bone formation. The product includes a BMP factor capable of inducing bone formation and at least one associated protein incapable of inducing bone formation independent of the BMP factor. The isolation and identification of the proteins encoded by the DNA of the present invention are not enabled by this disclosure.

Urist et al, Science 220: 680-686 (1983) reviews progress in the field of bone cell differentiation and growth factors.

Caplan and Syftestad, US Patent 4,608,199 discloses a process of extracting and purifying a bone protein capable of stimulating chondrogenesis. This protein is water soluble and acidic unlike that encoded by sequences of the present invention.

Nathanson et al, US Patent 4,681,763 is understood to disclose a method of recovering a material capable of inducing new bone and cartilage. This material is broadly characterized as an extract of demineralized bone and is deposited by precipitation onto a pliable support.

Sampath et al, PNAS, 84: 7109-7113 (1987) discloses isolation of a bone inductive protein having an apparent molecular weight of 22,000 daltons. Sequence information is not disclosed.

Evans et al, US Patent 4,737,578 discloses human inhibin. Proteins encoded by sequences of the present invention do share some homology with the inhibins, however they are different molecules.

Mason and Seeburg, US Patent 4,798,885 is also directed to human inhibin. Proteins encoded by sequences of the present invention do share homology with the inhibins, but are different molecules.

The present application claims filing dates which are earlier than the filing dates of the following references.

Kuberasampath and Rueger, U.S. Patent 4,968,590 contains bovine amino acid sequence of BMP-2 (see claim 11 of '590 and in the present application see Table I amino acids #98-#110) which is also present in human BMP-2 (see Table II amino acids #365-#377 of the present application). '590 does not teach or suggest the DNA sequences of the present invention and is not pertinent to the patentability thereof. This patent was filed on the same day as the present application and does not claim the benefit of any earlier filing dates as does the present application.

Oppermann et al, WO89/09788 Kuberasampath et al, WO89/09787 related to U.S. '590 discussed in the preceding paragraph disclose osteogenic proteins and devices. DNA sequences of the present invention are not disclosed.

Parsons et al, WO90/03733 discloses an osteogenically active protein. Amino acid sequence information is disclosed which corresponds to amino acid sequence of BMP-2 (BMP-2A) and BMP-4 (BMP-2B). DNA sequences as claimed in the present invention are not disclosed.

Respectfully submitted, -



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Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants

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GI 5160C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : E. Wang et al.,
 Serial No. : 07/721,847 Examiner : K FURMAN
 Filed : 14 JUNE 1991 Art Unit : 1814
 For : Novel BMP PRODUCTS

February 15, 1993

Hon. Commissioner of
 Patents and Trademarks
 Washington, DC 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on February 16, 1993
Alan J. Frazier

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with the provisions of 37 C.F.R. §§ 1.56 and 1.97, and 1.98(d) the publications and/or patents listed on the attached form PTO-1449 are cited for consideration by the Examiner in connection with the examination of the above-identified patent application. It is understood that the references need not be provided herewith as they have been previously submitted to the Office in the prior parent application.

In accordance with the provisions of 37 C.F.R. §1.97, this statement is being filed (CHECK ONE):

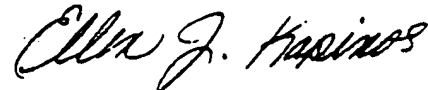
- (1) within three (3) months of the Filing Date or before the mailing date of the First Office Action on the merits; or
- (2) after the period defined in (1) but before the mailing date of a Final Rejection or Notice of Allowance, and the requisite Certification or fee under Rule 1.17(p), namely \$200.00, is included herein; or
- (3) after the mailing date of a Final Rejection or Notice of Allowance but before the payment of the Issue Fee, and the requisite Certification, petition, and petition fee are included herein.

WANG ET AL
USSN 07/721,847
February 15, 1993
PAGE2

It is respectfully requested that each of the documents shown on the attached form PTO-1449 be made of record in this application.

The Commissioner is authorized to charge the \$200.00 fee to our Deposit Account, No. 07-1060 and any additional fees deemed necessary to said Deposit Account.

Respectfully submitted,



Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants
(617)-876-1170



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Elizabeth Wang, John Wozney, Vicki Rosen
Serial No. : 07/655,579
Examined : M. Allen
Filed : March 18, 1991
Art Unit : 1812
For : NOVEL BMP-2 PRODUCTS

COPY

March 2, 1993

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on MARCH 17, 1993
Ellen J. Kojinas

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with the provisions of 37 C.F.R. §§ 1.56 and 1.97, 1.98(d) the publications and/or patents listed on the attached form PTO-1449 are cited for consideration by the Examiner in connection with the examination of the above-identified patent application. It is understood that the references need not be provided herewith as they have been previously submitted to the Office in the prior parent application.

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It is respectfully requested that each of the documents shown on the attached form PTO-1449 be made of record in this application.

Early examination and allowance of the present application are respectfully solicited.

Should any fee associated with the submission of this paper not be attached hereto as a check, the Commissioner is authorized to charge the missing fee to our Deposit Account, No. 07-1060. Any overpayments should be credited to said Deposit Account.

Respectfully submitted,

Legal Affairs
Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, Massachusetts 02140

Ellen J. Kapinos
Ellen J. Kapinos
Reg. No. 32,245
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GI5160

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

COPY

APPLICANT: Wang et al)
SERIAL NO.: 07/378,537)
FILED: July 11, 1989)
TITLE: DNA SEQUENCES)
ENCODING)
OSTEOINDUCTIVE)
PROTEINS)

GROUP ART UNIT: 185
EXAMINER: J. Ellis

October 7, 1991

Commissioner of Patents and Trademarks
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Dear Sir:

The following documents are submitted pursuant to 37 CFR 1.56 and 1.97. The documents described below are listed on accompanying PTO Form 1449 and copies of the references are submitted herewith.

Sen, US Patent 4,804,744 is understood to disclose a family of immunologically related osteogenic factors extracted from demineralized bone matrix. The disclosed amino acid sequences of these factors do not share any homology with the proteins encoded by sequences of the present invention and are therefore considered to be different proteins. Sen, European Publication 148155 (not enclosed) corresponds to the above-described US Patent 4,804,744.

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isolation of a mixture of proteins having a molecular weight of 1,000-100,000 daltons.

Urist, US Patent 4,761,471 and 4,789,732 are divisionals of Urist 4,619,989. A BMP factor capable of inducing bone formation and at least one associated protein incapable of inducing bone formation independent of the BMP factor are disclosed. The isolation and identification of the proteins encoded by the DNA of the present invention are not enabled by this disclosure.

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Evans et al, US Patent 4,737,578 discloses human inhibin. Proteins encoded by sequences of the present invention do share some homology with the inhibins, however they are different molecules.

Mason and Seeburg, US Patent 4,798,885 is also directed to

human inhibin. Proteins encoded by sequences of the present invention do share homology with the inhibins, but are different molecules.

Kuberasampath and Rueger, U.S. Patent 4,968,590 discloses bovine amino acid sequence of BMP-2A(BMP-2) (see claims 9, 10 and 12). '590 does not teach or suggest the DNA sequences of the present invention and is not pertinent to the patentability thereof.

Oppermann et al, WO89/09788 and Kuberasampath et al, WO89/09787 related to U.S. '590 discussed in the preceding paragraph disclose osteogenic proteins and devices. DNA sequences of the present invention are not disclosed.

Parsons et al, WO90/03733 discloses an osteogenically active protein. Amino acid sequence information is disclosed which corresponds to amino acid sequence of BMP-2A (BMP-2) and BMP-2B (BMP-4). DNA sequences as claimed in the present invention are not disclosed.

Luyten et al, J. Biol. Chem. 264:13377-13380 (1989) discloses osteogenin having amino acid sequences homologous to BMP-3. In fact, the end of the article notes the publication of Applicants' Science 242: 1528-1534(1988) article which published after the submission of the Luyten manuscript.

Oppermann et al, U.S. 5,011,691 is understood to be directed to osteogenic devices. BMP-2A amino acid sequence is disclosed, but there is no disclosure of the BMP DNA sequences of the present invention.

Kiefer et al, EP 409472 A1 discloses a protein which does not

Wang et al
USSN 07/378,537
Page 5

share homology with BMP-2A (BMP-2) or BMP-2B (BMP-4). This protein is noted however to share homology with the protein claimed in Sen EP0148155 discussed above.

Bentz et al, WO91/02744 discloses a purported bone-specific protein which does not share homology with BMP-2A(BMP-2) or BMP-2B(BMP-4).

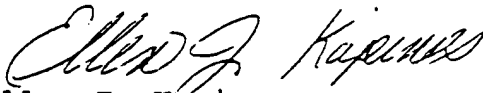
Murakami et al, EP416578A2 discloses *Xenopus laevis* bone morphogenic protein.

Oppermann et al, WO91/05802 is directed to an osteogenic protein, OP-1, which differs from BMP-2A(BMP-2) and BMP-2B(BMP-4).

Kiefer, CA 2,017,466 discloses bone calcification factor which does not share homology with BMP-2A(BMP-2) or BMP-2B(BMP-4).

Respectfully submitted,

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